

#### REMARKS

Claims 59-65, 67-76, and 78-90 are pending in the instant application. Claims 59-65, 67-76, 78-80, and 90 stand rejected under 35 U.S.C. § 112, second paragraph. Claims 59-65, 67-76, and 78-90 stand rejected under 35 U.S.C. § 102(a). Reconsideration of the claims in light of the amendments and remarks that follow is respectfully requested.

#### Oath or Declaration

The Examiner has objected to the Oath or Declaration on file as defective due to the presence of non-initialed alterations. A replacement Oath or Declaration is enclosed with this Amendment. Accordingly, withdrawal of this objection is respectfully requested.

#### 35 U.S.C. § 112, second paragraph

Claims 59-65, 67-76, 78-80, and 90 stand rejected under 35 U.S.C. § 112, second paragraph, as being vague and indefinite in their recitation of "about 30-60 seconds." In particular, the Examiner states that it is not clear whether "about" refers only to the lower limit of 30 seconds or to both the 30 and 60 second limits. As shown above, the claims have been amended to recited "about 30 to about 60 seconds" to remove any possible indefiniteness. Accordingly, withdrawal of the rejection under § 112, second paragraph, is respectfully requested.

#### 35 U.S.C. § 102(a)

Claims 81-85 stand rejected under 35 U.S.C. § 102(a) as being anticipated by Wittwer et al., Nucleic Acid Research, 17:11, 4353 (1989). A Katz type declaration under 37 C.F.R. §1.132 is enclosed with this Amendment to overcome this rejection. The declaration clarifies that any authors of the cited reference who are not listed inventors of the instant application did not contribute to the conception of the instant application but rather worked under the direction and supervision of the named inventors. Accordingly, as the inventive entities are identical, the cited reference cannot be considered prior art under § 102(a) and withdrawal of this rejection under § 102(a) is respectfully requested.

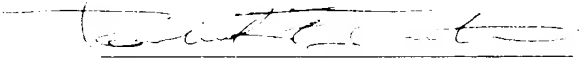
Claims 59-65, 67-76, and 78-90 stand rejected under 35 U.S.C. § 102(a) as being anticipated by Wittwer et al., Analytical Biochem., 186:328 (1990). A Katz type declaration under 37 C.F.R §1.132 is enclosed with this Amendment to overcome this rejection. The declaration clarifies that any authors of the cited reference who are not listed inventors of the instant application did not contribute to the conception of the instant application but rather worked under the direction and supervision of the named inventors. Accordingly, as the inventive entities are identical, the cited reference cannot be considered prior art under § 102(a) and withdrawal of this rejection under § 102(a) is respectfully requested.

### CONCLUSION

On the basis of the amendments and remarks presented herein, Applicants believe that this application is now in condition for immediate allowance. Applicants respectfully request that the Examiner pass this application to issue, and early notice of such is requested. This paper is filed under 37 C.F.R. section 1.34(a).

Respectfully submitted,  
DORSEY & WHITNEY LLP

Date: 11/27/02

  
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**Version Showing Changes Made**

59. (Amended) A method of subjecting a sample to rapid thermal cycling, said method comprising:

a) contacting a sample holder containing a sample with heated fluid, thereby raising the temperature of the sample to a first temperature, and holding the sample at about said first temperature for a first predetermined period of time;

b) contacting the sample holder with non-heated fluid, thereby lowering the temperature of the sample to a second temperature, and holding the sample at about said second temperature for a second predetermined period of time;

c) contacting the sample holder with heated fluid, thereby raising the temperature of the sample to a third temperature, and holding the sample at about said third temperature for a third predetermined period of time;

wherein steps a) through c) are completed in about 30 [-] to about 60 seconds; and wherein said sample holder has a thermal mass which provides for completing said cycle in about 30 [-] to about 60 seconds.

70. (Amended) A method of amplifying a nucleic acid, said method comprising:

a) heating a sample holder containing a sample comprising a nucleic acid and amplification primer, thereby raising the temperature of the sample to a first temperature, and holding the sample at about said first temperature for a first predetermined period of time to denature said double-stranded nucleic acid;

b) cooling the sample holder, thereby lowering the temperature of the nucleic acid sample to a second temperature, and holding the sample at about said second temperature for a second predetermined period of time to anneal said amplification primer;

c) heating the sample holder, thereby raising the temperature of the nucleic acid sample to a third temperature, and holding the sample at about said third temperature for a third predetermined period of time to allow amplification of said nucleic acid;

d) repeating steps a) through c), wherein steps a) through c) are completed in about 30 [-] to about 60 seconds;

wherein said sample holder has a thermal mass which provides for completing said cycle in about 30 [-] to about 60 seconds.

### Appendix of Pending Claims

59. (Twice Amended) A method of subjecting a sample to rapid thermal cycling, said method comprising:

a) contacting a sample holder containing a sample with heated fluid, thereby raising the temperature of the sample to a first temperature, and holding the sample at about said first temperature for a first predetermined period of time;

b) contacting the sample holder with non-heated fluid, thereby lowering the temperature of the sample to a second temperature, and holding the sample at about said second temperature for a second predetermined period of time;

c) contacting the sample holder with heated fluid, thereby raising the temperature of the sample to a third temperature, and holding the sample at about said third temperature for a third predetermined period of time;

wherein steps a) through c) are completed in about 30 to about 60 seconds; and

wherein said sample holder has a thermal mass which provides for completing said cycle in about 30 to about 60 seconds.

60. The method of Claim 59, wherein steps a) through c) are repeated.

61. The method of Claim 59 or 60, wherein said sample holder is one of a plurality of sample holders.

62. The method of Claim 59 or 60, wherein the first predetermined period of time is about 8 seconds or less.

63. The method of Claim 62, wherein the first predetermined period of time is less than 1 second.

64. The method of Claim 59 or 60, wherein said lowering in step b) occurs in about 25 seconds or less.

65. The method of Claim 59 or 60, wherein said lowering in step b) occurs at an average rate of between at least about 1.5 °C per second and up to about 4.1 °C per second.

67. The method of Claim 59 or 60, wherein the difference between said first and said second temperature is up to about 42 °C.

68. The method of Claim 59 or 60, wherein the second predetermined period of time is about 5 seconds or less.

69. The method of Claim 68, wherein the second predetermined period of time is less than 1 second.

70. (Twice Amended) A method of amplifying a nucleic acid, said method comprising:

a) heating a sample holder containing a sample comprising a nucleic acid and amplification primer, thereby raising the temperature of the sample to a first temperature, and holding the sample at about said first temperature for a first predetermined period of time to denature said double-stranded nucleic acid;

b) cooling the sample holder, thereby lowering the temperature of the nucleic acid sample to a second temperature, and holding the sample at about said second temperature for a second predetermined period of time to anneal said amplification primer;

c) heating the sample holder, thereby raising the temperature of the nucleic acid sample to a third temperature, and holding the sample at about said third temperature for a third predetermined period of time to allow amplification of said nucleic acid;

d) repeating steps a) through c), wherein steps a) through c) are completed in about 30 to about 60 seconds;

wherein said sample holder has a thermal mass which provides for completing said cycle in about 30 to about 60 seconds.

71. The method of Claim 70, wherein said sample further comprises a nucleic acid polymerizing enzyme.

72. The method of Claim 70, wherein said sample holder is one of a plurality of sample holders.

73. The method of Claim 70, wherein the first predetermined period of time is less than 1 second.

74. The method of Claim 70, wherein said lowering in step b) occurs in about 25 seconds or less.

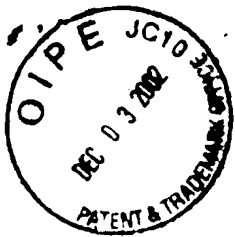
75. The method of Claim 74, wherein said lowering in step b) occurs in about 9 seconds.

76. The method of Claim 70, wherein said lowering in step b) occurs at an average rate of between at least about 1.5 °C per second and up to about 4.1 °C per second.

78. The method of Claim 70, wherein the difference between said first and said second temperature is up to about 42 °C.

79. The method of Claim 70, wherein the second predetermined period of time is about 5 seconds or less.
80. The method of Claim 79, wherein the second predetermined period of time is less than 1 second.
81. A method of subjecting a sample to rapid thermal cycling to amplify a nucleic acid, said method comprising:
- a) raising the temperature of a sample to a first temperature and holding the sample at about said first temperature for a first predetermined period of time;
  - b) lowering the temperature of the sample to a second temperature at a rate at least about 1.5 °C per second and holding the sample at about said second temperature for a second predetermined period of time.
82. The method of Claim 81, further comprising:
- c) raising the temperature of the sample to a third temperature intermediate to said first and second temperatures and holding the sample at about said third temperature for a third predetermined period of time.
83. The method of Claim 81 or 82, wherein the steps are repeated.
84. The method of Claim 81 or 82, wherein said lowering in step b) is at a rate of up to about 4.1 °C per second.
85. The method of Claim 81 or 82, wherein the difference between said first and said second temperature is up to about 42 °C.
86. The method of Claim 81 or 82, wherein the first predetermined period of time is about 8 seconds or less.
87. The method of Claim 81 or 82, wherein the first predetermined period of time is less than 1 second.
88. The method of Claim 81 or 82, wherein the second predetermined period of time is about 20 seconds or less.
89. The method of Claim 81 or 82, wherein the second predetermined period of time is less than 1 second.

90. The method of Claim 70, further comprising the step;  
e) detecting the amplification products by fluorescence.



**PATENT**

Attorney Docket No.:A-67724-8/RFT/SPL/469322-00005

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Wittwer, *et al.*

Examiner: Marschel, A.

Group Art Unit: 1631

Serial No. 09/132,156

**CERTIFICATE OF MAILING**

I hereby certify that this correspondence, including listed enclosures, is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, DC 20231.

Date: 11/27/02

Signed:   
Steven Lendaris

Filed: August 11, 1998

For: Method for Rapid  
Thermal Cycling of  
Biological Samples

**DECLARATION UNDER 37 C.F.R. § 1.132**

Commissioner for Patents  
Washington D.C. 20231

Sir:

I, Carl Wittwer, hereby declares as follows:

1. I am one of the named inventors of the invention claimed in the above-identified application.
2. I am a co-author of "Minimizing the Time Required for DNA Amplification by Efficient Heat Transfer to Small Samples" Anal. Biochem., 186(2): 328-331 (1990), wherein Fillmore, GC and Garling, DJ are also co-authors.
3. Fillmore, GC held the position of Laboratory Technologist at the time of his contribution.
4. Fillmore, GC did not contribute to the conception of the invention disclosed in the above-cited application. He designed and performed experiments under my direction and supervision, thereby contributing to the reduction to practice of the invention.



5. Garling, DJ held the position of Pathology Resident at the time of his contribution.

6. Garling, DJ did not contribute to the conception of the invention disclosed in the above-cited application. He designed and performed experiments under my direction and supervision, thereby contributing to the reduction to practice of the invention.

7. I am a co-author of "Automated Polymerase Chain Reaction in Capillary Tubes with Hot Air" Nucleic Acids Research, 17(11): 4353-4357 (1989), wherein Fillmore, GC and Hillyard, DR are also co-authors.


8. Fillmore, GC held the position of Laboratory Technologist at the time of his contribution.

9. Fillmore, GC did not contribute to the conception of the invention disclosed in the above-cited application. She designed and performed experiments under my direction and supervision, thereby contributing to the reduction to practice of the invention.

10. Hillyard, DR is one of the named inventors of the invention claimed in the instant application.

11. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful, false statements may jeopardize the validity/enforceability of the application or any patent issued thereon.

Date: Nov. 13 2002

  
Carl Wittwer

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